REMARKS

Status of claims

Claims 1 and 25 have been amended as suggested by the Examiner. It is believed that this amendment places the claims in condition for allowance or else places them in better condition for appeal, and that the amendment should therefore be entered.

Claims 1-15, 18, 22, 23, and 25-40 are pending; all have been rejected.

Claim Rejections - 35 U.S.C. § 112, first paragraph

Claims 1, 4-15, 18, 22, 23, 38, and 39 have been rejected under the first paragraph of 35 U.S.C. § 112 for failure to enable one skilled in the art to practice the invention commensurate in scope with the claims.

The Examiner first states that the specification "does not reasonably provide enablement for any and all anti-infective agents and any and all microorganisms 'susceptible' to the anti-infective agents." This rejection is respectfully traversed.

Independent claims 1 and 15 are restricted to a group of anti-infective agents "selected from the group consisting of betalactams, fluoroquinolones, macrolides and betalactamase inhibitors." This is a limited group of anti-infective agents well exemplified in the specification, and the Examiner has given no reason to believe that the present invention would not be operative with any of these anti-infective agents.

Claim 1 is likewise limited to microorganisms which are "useful in preventing or minimizing adverse effects of said anti-infective agent." Numerous examples of such microorganisms are given in the specification, and similar lists are given in the prior art of record. The Examiner has given no reason other than a generalized concern about the vagaries of "living beings" for this rejection. The types of

microorganisms which are useful in preventing or minimizing the adverse effects of the enumerated antibiotics are known in the art, and it is known that they perform their intended purpose when administered separately from the anti-infectives. As set out in the specification, describing the prior art:

> To prevent diarrhea, organisms are given along with the anti-infective agents. This requires consumption of a minimum of two different drugs, i.e. an anti-infective agent and an organism. This decreases compliance of a patient. Page 4, lines 11-14.

The only issue is therefore whether the Examiner has provided a prima facie case that these microorganisms will not perform their function when administered in a single dose with the anti-infective in accordance with the present invention. Applicants have shown numerous combinations of anti-infectives and microorganisms, all of which do work in the combination. The Examiner has shown no reason to believe that a microorganism which is useful in preventing or minimizing adverse effects of the enumerated antibiotics will not be also be useful when formed into a fixed dose oral pharmaceutical formulation in accordance with the invention as claimed in these claims.

The other independent claim subject to this rejection is claim 38. That claim is limited to anti-infective agents "capable of causing adverse effects caused by destruction of commensals" and to microorganisms "useful in preventing or minimizing the adverse effects of said anti-infective agent." It further requires "a protective barrier between the anti-infective agent and the microorganism, *wherein the anti-infective agent would destroy the viability of the microorganism in the dry formulation in less than three months* in the absence of the protective barrier, and *wherein the protective barrier protects the susceptible microorganism from the effect*

of the anti-infective agent to maintain the susceptible microorganism in a viable form for a period of at least three months. The specification gives numerous examples of such anti-infective agents and microorganisms, and it is believed that the use of a protective barrier of the invention in such formulations, as called for in the claim, is fully enabled by the specification. Again, the anti-infectives and microorganisms are not, per se, the claimed invention; rather it is the claimed combination, which allows them to be stored and ingested together as a single formulation.

The Examiner has also objected to the word "susceptible" as vague and indefinite. It is submitted that this term is well-known in the art and is widely used to describe the effect of an antibiotic on a microorganism. The concept of susceptible and resistant strains of bacteria is fundamental to the pharmacology of anti-bacterial drugs. It is not a vague term as suggested by the Examiner, but rather a generally-used term in the art. It is also used consistently throughout the present specification. If the Examiner is more comfortable with the alternative terms "sensitive" or "not resistant", however, he is requested to call applicants' undersigned attorney.

Claim Rejections - 35 U.S.C. § 112, second paragraph

All of the pending claims have been rejected under the second paragraph of 35 U.S.C. § 112 as being indefinite for failure to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Claims 1 and 15 have been amended as suggested to replace the word "it".

The word "susceptible" is not vague and indefinite, as suggested by the Examiner, for the reasons set forth in the prior section. It is a widely used and accepted term in the art, and the terms "susceptible," "resistant" and "antibiotic" are found in thousands of patents. Merely by way of example, Nakane, U.S. Patent No.

6,750,038 says, "When a species of bacteria is challenged by an antibiotic, susceptible members die while those which are resistant, survive, reproduce and pass on their resistance." Col. 1, lines 33-35.

Finally, the Examiner objects to describing anti-infective agents as "capable of causing adverse effects caused by destruction of commensals" (claim 38) and microorganisms as "useful in preventing or minimizing the adverse effects of said anti-infective agent" (claims 1, 25 and 38). It is submitted that the destruction of commensals by antibiotics and the use of beneficial microorganisms to counteract the effects of this destruction are so well known in the art that the foregoing language clearly defines for those skilled in the art what applicants' invention encompasses. This is all that is required of the claims.

Claim Rejections - 35 U.S.C. § 102

Claims 38 and 39 were rejected under 35 U.S.C. § 102(b) as anticipated by FR 6855 and as anticipated by FR 5247. Both French patents relate to formulations of tetracycline and resistant microorganisms.

This rejection is respectfully traversed. Claim 38 calls for "a protective barrier between the anti-infective agent and the microorganism, *wherein the anti-infective agent would destroy the viability of the microorganism in the dry formulation in less than three months* in the absence of the protective barrier, and *wherein the protective barrier protects the susceptible microorganism from the effect of the anti-infective agent to maintain the susceptible microorganism in a viable form for a period of at least three months.*"

FR 6855 lacks a protective barrier. It therefore does not anticipate claim 38 or its dependent claim 39.

FR 5247 utilizes a barrier in the form of gelatin, colophane, gluten or isokeratol. However, reading FR 5247 in view of FR 6855 suggests that placing a barrier between the anti-infective agent and the micro-organisms is not required, and that the anti-infective agent would not destroy the viability of the microorganism in the dry formulation in less than three months in the absence of the protective barrier, as required by claim 38. Given the bacteriostatic nature of tetracycline, it is reasonable to assume that it would not be likely to destroy the viability of the microorganisms in the dry formulation of FR 5247 even if the barrier were omitted. It is thus submitted that claim 38 is not anticipated by FR 5247.

Claim rejection - 35 U.S.C. § 103

All the claims were rejected under 35 U.S.C. § 103(a) as being unpatentable over FR 5247 in view of FR 6855 and further in view of Black et al. "One of ordinary skill in the art would have been motivated to use ampicillin instead of tetracycline since Black yielded such beneficial results."

Black discloses a study in which one group was given beneficial microorganisms two hours after each administration of ampicillin. This is precisely the situation described in the specification, and quoted above, at page 4, lines 11-14:

> To prevent diarrhea, organisms are given along with the anti-infective agents. This requires consumption of a minimum of two different drugs, i.e. an anti-infective agent and an organism. This decreases compliance of a patient.

It would not have been obvious to "use ampicillin instead of tetracycline" as suggested by the Examiner, for a number of reasons. As discussed above, the two cited French references, taken together, suggest that a barrier coating is not necessary to produce a stable tablet containing tetracycline and a microorganism.

Therefore, whatever the reasons for providing a coating of gelatin, colophane, gluten or isokeratol, the FR 5247 reference would not have suggested to one skilled in the art that it would solve the long-standing problems of non-compliance with separate dosages of ampicillin and microorganisms, or of loss of viability of ampicillin when packaged with the microorganism.

It may also be noted that many antibiotics other than tetracycline were known at the time of filing of the two French references (1966 for FR 5247 and 1967 for FR 6855):

Sulfonamide	1930
Chloramphenicol	1947
Tetracycline	1948
Erythromycin	1952
Penicillin V	1956
Methicillin	1960
Ampicillin	1961
Cloxacillin	1962

(From Encyclopedia : Timeline of antibiotics downloaded from http://www.iridis.com/glivar/Timeline_of_antibiotics.)

That only the bacteriostatic oral antibiotic tetracycline was disclosed, and none of the bacteriocidal antibiotics from this list was disclosed, is telling. The problem of diarrhea induced by the penicillins, like ampicillin, was well-known since their introduction, yet the solution developed by applicants eluded the art until the present invention.

Applicants' attorney thanks the Examiner for responding to his requests for a telephone interview. In a brief telephone discussion today, January 12, 2005, the issues discussed herein were briefly mentioned, and the Examiner indicated that resolving the issues would be better accomplished following a request for continued examination. No specific claims were discussed, other than an indication by the Examiner as to his dislike of the "capable of" language in claim 38. No agreement was sought or reached with respect to any of the issues in the case.

Should the Examiner not be prepared to allow all of the claims following entry of the request for continued examination, he is again requested to call Applicants' undersigned attorney to arrange an interview.

Respectfully submitted,

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